

### **REMARKS**

Claims 40 - 52 are currently pending and under examination. Claims 40 - 52 stand rejected. By this Amendment, claims 45 – 47 and 51 have been amended. Accordingly, upon entry of this Amendment, claims 40 - 52, as amended, will be pending and under examination. Claims 40 and 47 are independent.

Claim 51 has been amended to include the “ramification-extension amplification method (RAM).” Support for this amendment may be found *inter alia* in the subject application, as originally-filed, at page 62, line 14 through page 64, line 2.

### **Claim Objections**

On page 2 of the June 3, 2004 Office Action, the Examiner objected to claim 45 because of certain informalities. The Examiner alleged that the term, “RAM” is an abbreviation and can only be used after the phrase appears once. The Examiner required appropriate correction.

In order to expedite the prosecution of the subject application, and without conceding either the correctness of the Examiner’s position or the need for amendment for patentability reasons, Applicants have amended claim 45 to recite “ramification-extension amplification method (RAM)” the first time the term appears, as requested. Such changes are fully supported in the application, as originally-filed.

### **Drawings**

On page 2 of the June 3, 2004 Office Action, the Examiner objected to the drawing for Figure 13. Specifically, the Office Action stated that there was no label for “Figure 13.”

The Examiner is thanked for calling attention to this point. The drawing has been carefully reviewed. Suitable drawing changes have been proposed by way of the accompanying Request for Approval to Make Drawing Changes, two copies of which are also submitted herewith.

Accordingly, favorable reconsideration and withdrawal of these objections is respectfully requested.

**Rejection Under 35 U.S.C. § 112, Second Paragraph**

On page 2 of the June 3, 2004 Office Action the Examiner rejected claims 47 – 52 under U.S.C. § 112, second paragraph, as indefinite for allegedly failing to particularly point out and distinctly claim the subject matter. The Examiner specifically alleged that claim 47 was rejected as vague because it appears that the contacting step recited in (a) of the claim and the adding step in (b) of the claim are the same step. The Examiner requested clarification.

In order to expedite the prosecution of the subject application, and without conceding either the correctness of the Examiner's position or the need for amendment for patentability reasons, Applicants have amended claim 47 to remove the adding step (b) of the claim and added the limitation of "comprising a first primer and a second primer" to step (a) to preserve the antecedent basis for steps (a)(i) and (a)(ii). Such changes are fully supported in the application, as originally-filed.

**Rejection Under 35 U.S.C. § 102(b)**

On page 3 of the June 3, 2004 Office Action the Examiner rejected claims 47, 48, 51 and 52 under U.S.C. § 102(b), as anticipated by Wang et al., (US Patent No. 5,567,583, published on October 22, 1996)("Wang"). Regarding claim 47, the Examiner alleged that Wang discloses contacting the nucleic acid with an oligonucleotide primer pair comprising a first primer (i.e., the first primer taught by Wang) and a second primer (i.e., the oligonucleotide taught by Wang) under conditions that allow hybridization between complementary sequences in the target nucleic acid and the oligonucleotide primer pair, wherein (i) the first primer of the pair comprises (A) a first sequence that is complementary to the target nucleic acid (i.e., the first primer sequence taught by Wang), (B) a second sequence that is complementary to the second primer of the pair (i.e., at least 5 consecutive nucleotides of said first primer taught by Wang), and (C) a signal generating moiety (i.e., the first fluorophore taught by Wang); (ii) the second primer of the pair (i.e., the oligonucleotide taught by Wang) comprises (A) a sequence that is complementary to the first primer (i.e., at least 5 consecutive nucleotides fully complementary to at least 5 consecutive nucleotides of said first primer taught by Wang); and (B) a moiety capable of quenching, masking or inhibiting the activity of the signal generating moiety when located adjacent to, or in close proximity to the signal generating moiety (i.e., the second fluorophore

taught by Wang); and (iii) when the first primer and the second primer are bound to one another, the signal is inhibited (i.e., one of the said first and second fluorophores being a donor fluorophore and the other being an acceptor fluorophore and causing fluorescence energy transfer); adding a single stranded oligonucleotide primer comprising sequences complementary to the target nucleic acid (i.e., the second primer taught by Wang); adding a DNA polymerase; and amplifying the target nucleic acid and separating the signal generating moiety (i.e., the donor fluorophore taught by Wang) and the quenching, masking or inhibitory moiety (i.e., an acceptor fluorophore taught by Wang); thereby generating a signal, wherein detection thereof indicates the presence of the target nucleic acid in the sample (see columns 19 and 20, claims 1 and 3, column 3, second paragraph, and Figure 1).

The Examiner further alleged that regarding claim 48, Wang teaches that the signal generating moiety is a fluorescent agent (see columns 19 and 20, claims 1 and 3). Finally, the Examiner alleged that regarding claims 51 and 52, Wang teaches that the target nucleic acid is amplified using polymerase chain reaction (see column 2, lines 32 – 39).

Applicants respectfully disagree with the Examiner's rejections. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California* 814 F.2d 628, 631 (Fed Cir. 1987). Claim 47, the only independent claim rejected under U.S.C. §102(b), has the following limitations, as amended herein: (a) contacting the nucleic acid with an oligonucleotide primer pair under conditions that allow hybridization between complementary sequences in the target nucleic acid and the oligonucleotide primer pair; (i) the first primer of the pair comprises (A) a first sequence that is complementary to the target nucleic acid, (B) a second sequence that is complementary to the second primer of the pair, and (C) a signal generating moiety; (ii) the second primer of the pair comprises (A) a sequence that is complementary to the first primer and (B) a moiety capable of quenching, masking or inhibiting the activity of the signal generating moiety when located adjacent to, or in close proximity to the signal generating moiety; and (iii) when the first primer and the second primer are bound to one another, the signal is inhibited; (b) adding a single stranded oligonucleotide primer comprising sequences complementary to the target nucleic acid; (c) adding a DNA polymerase; and (d) amplifying the target nucleic acid and separating the signal generating moiety and the quenching, masking or

inhibitory moiety, thereby generating a signal, wherein detection thereof indicates the presence of the target nucleic acid in the sample.

Applicants maintain that Wang does not teach limitation of step (a) of claim 47 (i.e., contacting the nucleic acid with an oligonucleotide primer pair under conditions that allow hybridization between complementary sequences in the target nucleic acid and the oligonucleotide primer pair). Wang teaches the use of a blocking oligonucleotide which functions to prevent binding of the double-stranded primer to the target nucleic acid (column 5, lines 30 – 36), therefore the primer of the Wang method can only bind to the target nucleic acid as a single-stranded entity (Figure 1). In contrast, claim 47 recites that the target nucleic acid and the primer pair are contacted under conditions that allow hybridization between the target nucleic acid and the primer pair. Accordingly, Wang does not anticipate claim 47 because Wang does not teach each and every element of the claim. Specifically, Wang does not teach the limitation of step (a) of claim 47.

Furthermore, Applicants maintain that Wang does not teach limitation (a)(ii)(B) (i.e., a moiety capable of quenching, masking or inhibiting the activity of the signal generating moiety when located adjacent to, or in close proximity to the signal generating moiety) or limitation (a)(iii) (when the first primer and the second primer are bound to one another, the signal is inhibited). The Examiner alleged that the acceptor fluorophore taught by Wang anticipates the “quenching moiety” limitation, however, Wang does not teach that the acceptor fluorophore actually quenches that signal of the donor fluorophore. Indeed, all of the examples in Wang disclose a donor:acceptor pair that displays a signal when in close proximity to each other and that the signal decreases upon amplification of the target nucleic acid (Example IV, column 12, lines 59 – 63; Figure 5). This is indirect contrast to the primer pair of the claimed invention whereby the primer pair displays no signal when the first primer and the second primer are bound to one another and only exhibits a signal upon amplification of the target nucleic acid (i.e., when the signal generating moiety is separated from the inhibitory moiety). Accordingly, Wang does not anticipate claim 47 because Wang does not teach each and every element of the claim. Specifically, Wang does not teach the limitation of steps (a)(ii)(B) and (a)(iii) of claim 47.

Finally, Wang does not teach limitation (d) of claim 47 (i.e., amplifying the target nucleic acid and separating the signal generating moiety and the quenching, masking or inhibitory moiety, thereby generating a signal, wherein detection thereof indicates the presence of the target nucleic acid in the sample). As stated above, Wang discloses a donor:acceptor pair that displays a signal when in close proximity to each other and whose signal decreases upon amplification of the target nucleic acid. Therefore, the end point measurement at the conclusion of the amplification process is exactly opposite what would be measured at the conclusion of the amplification process recited in claim 47. While performing the Wang method, one would have to measure a decrease in signal, which is inherently ambiguous and not as advantageous as measuring an increase in signal. The decrease in signal could mean that one has a positive result or it could indicate that the assay did not adequately perform. Accordingly, Wang does not anticipate claim 47 because Wang does not teach each and every element of the claim. Specifically, Wang does not teach the limitation of step (d) of claim 47.

For the reasons stated above, Applicants maintain that a the statutory requirements of a U.S.C. §102(b) rejection have not been met. Therefore, the 35 U.S.C. 102(b) rejection should be withdrawn.

#### **Rejections Under 35 U.S.C. § 103(a)**

On page 5 of the June 3, 2004 Office Action the Examiner rejected claims 40 - 42, 45 and 46 under U.S.C. §103(a), as unpatentable over Zhang et al. (US Patent No. 5,942,391, published on August 24, 1999)(“Zhang”) in view of Wang.

The Examiner alleged that Zhang teaches RAM to amplify a target nucleic acid using a circular oligonucleotide probe (claim 1 in columns 67 – 69 and Figure 1) as recited in (a) of independent claim 40.

However, the Examiner acknowledged that Zhang does not disclose a primer pair comprising a first primer and a second primer having the characteristics recited in sections (i), (ii) and (iii) or detecting a signal which is generated by separating the signal generating moiety and the quenching, masking or inhibitory moiety as recited in claim 40. The Examiner further acknowledged that Zhang does not teach that the signal generating moiety is a fluorescent agent

as recited in claim 42. The Examiner cited Wang discussed *supra*, to allegedly overcome this deficiency. The Examiner then concluded that it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in independent claim 40, in view of the patents of Zhang and Wang.

Applicants respectfully disagree that it would have been obvious to perform the method recited in claim 40, in view of the patents of Zhang and Wang. "A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed.Cir. 1983), *cert. denied*, 469 U.S. 841 (1984); MPEP § 2141.02. For the reasons discussed *supra*, it would not have been obvious to perform the method of claim 40 in view of the method of Wang, since the Wang method, when considered in its entirety, produces a result (i.e., decrease in signal detected upon amplification of the target nucleic acid) that is completely opposite to the method taught in claim 40 (i.e., an increase in the signal upon amplification of the target nucleic acid). Furthermore, the increase in signal in the method of claim 40 actually teaches away from the combined Zhang and Wang methods.

Furthermore, Wang teaches the use of a blocking oligonucleotide which functions to prevent binding of the double-stranded primer to the target nucleic acid, therefore the primer of the Wang method can only bind to the target nucleic acid as a single-stranded entity. Claim 40 recites that the target nucleic acid and the primer pair are contacted under conditions that allow hybridization between the target nucleic acid and the primer pair. Accordingly, it would not have been obvious to perform the method of claim 40 in the presence of a blocking oligonucleotide, which would only serve to compete with the second primer of the primer pair. This would lead to the adverse result of generating a signal in the absence of DNA amplification, instead of an increase in signal in the presence of DNA amplification. Therefore, it would not have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 40, in view of the patents of Zhang and Wang and the 35 U.S.C. 103(a) rejections should be withdrawn.

On page 10 of the June 3, 2004 Office Action the Examiner rejected claim 43 under U.S.C. §103(a), as unpatentable over Zhang in view of Wang as applied to claims 40-42, 45 and

46 above, and further in view of Heller (US Patent No. 5,532,129, published on July 2, 1996)(“Heller”).

The Examiner relied on the teachings of Zhang and Wang, as discussed *supra*. However, the Examiner acknowledged that neither Zhang nor Wang disclose that the signal generating moiety (i.e., donor) is a chemiluminescent agent as recited in claim 43. The Examiner cited Heller to allegedly overcome the deficiencies.

The Examiner alleged that Heller teaches that either a fluorophore or a chemiluminescent group is used as donor for non-radiative energy transfer (column 3, second paragraph). For the reasons discussed *supra*, Applicants maintain that it would not have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 43, in view of the patents of Zhang and Wang. Furthermore, the deficiencies are not cured by the inclusion of Heller. Therefore, the 35 U.S.C. 103(a) rejection should be withdrawn.

On page 12 of the June 3, 2004 Office Action the Examiner rejected claim 44 under U.S.C. §103(a), as unpatentable over Zhang in view of Wang and Heller as applied to claims 40-43, 45 and 46 above, and further in view of Segev (US Patent No. 5,437,977, published on August 1, 1995)(“Segev”).

The Examiner relied on the teachings of Zhang, Wang and Heller as discussed *supra*. However, the Examiner acknowledged that Zhang, Wang and Heller do not disclose that the signal generating moiety is an enzyme or enzyme substrate as recited in claim 44. The Examiner cited Segev to allegedly overcome the deficiencies.

The Examiner alleged that Segev teaches that non-radiative transfer is finished by a suitable chemiluminescent catalyst such as peroxidase and luciferase and a suitable absorber/emitter (column 7, last paragraph and column 8, first paragraph). For the reasons discussed *supra*, Applicants maintain that it would not have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 44, in view of the patents of Zhang, Wang and Heller. Furthermore, the

deficiencies are not cured by the inclusion of Segev. Therefore, the 35 U.S.C. 103(a) rejection should be withdrawn.

On page 13 of the June 3, 2004 Office Action the Examiner rejected claim 49 under U.S.C. §103(a), as unpatentable over Wang as applied to claims 47, 48, 51 and 52 above, and further in view of Heller.

The Examiner relied on the teachings of Wang, as discussed *supra*. However, the Examiner acknowledged that Wang does not disclose that the signal generating moiety (i.e., donor) is a chemiluminescent agent as recited in claim 49. The Examiner cited Heller to allegedly overcome the deficiencies.

The Examiner alleged that Heller teaches that either a fluorophore or a chemiluminescent group is used as donor for non-radiative energy transfer (column 3, second paragraph). For the reasons discussed *supra*, Applicants maintain that it would not have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 49, in view of the patent of Wang. Furthermore, the deficiencies are not cured by the inclusion of Heller. Therefore, the 35 U.S.C. 103(a) rejection should be withdrawn.

On page 14 of the June 3, 2004 Office Action the Examiner rejected claim 50 under U.S.C. §103(a), as unpatentable over Wang and Heller as applied to claims 47, 48, 51 and 52 above, and further in view of Segev.

The Examiner relied on the teachings of Wang and Heller as discussed *supra*. However, the Examiner acknowledged that Wang and Heller do not disclose that the signal generating moiety is an enzyme or enzyme substrate as recited in claim 50. The Examiner cited Segev to allegedly overcome the deficiencies.

The Examiner alleged that Segev teaches that non-radiative transfer is finished by a suitable chemiluminescent catalyst such as peroxidase and luciferase and a suitable absorber/emitter (column 7, last paragraph and column 8, first paragraph). For the reasons discussed *supra*, Applicants maintain that it would not have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 50, in view of the patents of Wang and Heller. Furthermore, the deficiencies are



not cured by the inclusion of Segev. Therefore, the 35 U.S.C. 103(a) rejection should be withdrawn.

### **Double Patenting Rejection**

On page 16 of the June 3, 2004 Office Action the Examiner provisionally rejected claims 40 – 52 under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 1, 2, 5-9, and 43-52 of copending Application No. 10/719,480. The Examiner acknowledged that the conflicting claims were not identical but alleged that they were not patentably distinct from each other. Applicants will consider filing a terminal disclaimer in compliance with 37 C.F.R. 1.321(c) showing that the conflicting copending application and instant application are commonly owned, upon the Examiner's indication of allowable claims.

### **CONCLUSION**

Applicant respectfully submits that this application is in condition for allowance. Early and favorable action is earnestly solicited. No additional fees, other than the fees identified herein, are deemed necessary in connection with the filing of this Amendment. However, if any additional fees are due the amount of such fee may be charged to Deposit Account No. 19-4709.

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